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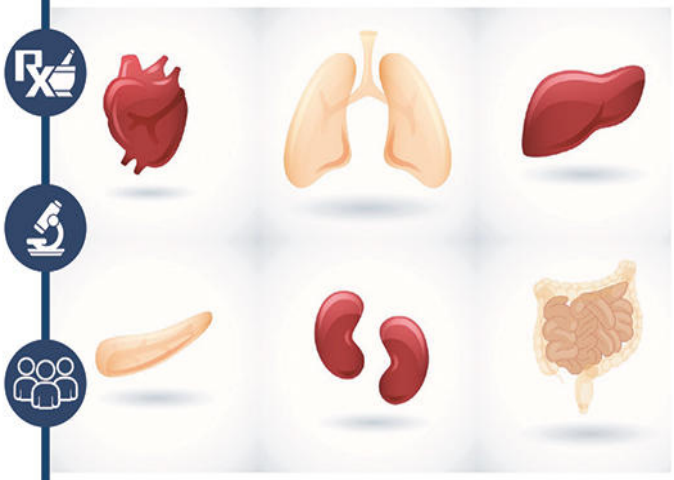

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Vitamin D deficiency is common in kidney transplant recipients, but is not associated with infections after transplantation

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Clin Transplant

Title: Vitamin D deficiency is common in kidney transplant recipients, but is not associated with infections after transplantation

Abstract: The relevance of vitamin D for infections after kidney transplantation is poorly defined. 25-OH vitamin D (25-OHD) levels of 135 kidney transplant recipients, enrolled in the Swiss Transplant Cohort Study, were determined peri-transplant and 6 months post-transplant. Logistic regression was used to address associations of 25-OHD and overall infections and bacterial infections, respectively. For the first 6 months post-transplant, 25-OHD peri-transplant, and for the second period (after 6 to 30 months post-transplant), 25-OHD at 6 months post-transplant was considered. Vitamin D deficiency was common peri-transplant and remained highly prevalent 6 months after transplantation despite frequent supplementation. Median 25-OHD levels increased from 12.0ng/ml (IQR 5.3-19.5) peri-transplant to 16.5ng/ml (IQR 10.6-22.6) 6 months post-transplant (P=0.005). We did not detect a significant association between 25-OHD and overall infections (adjusted odds ratio (aOR) 1.05, 95% confidence interval (95%CI) 0.44-2.51; aOR 0.67, 95%CI 0.31-1.43) or bacterial infections (aOR 0.79, 95%CI 0.32-1.96; aOR 0.79, 95%CI 0.35-1.75) for the first and second period. To conclude, at both time points vitamin D deficiency was observed in more than 50% of kidney recipients, albeit an increase in 25-OHD in the longitudinal course was observed. No significant association of 25-OHD and infections was detected.

Key words: kidney transplantation, vitamin D, infections, infectious disease medicine

Introduction

Vitamin D deficiency has been reported to be frequent among individuals with chronic renal failure [1]. Ultraviolet light exposure of the skin is considered as the most relevant source of vitamin D. Vitamin D itself is biologically not active and requires two hydroxylation steps for activation. In the liver an initial hydroxylation occurs resulting in 25-OH vitamin D (25-OHD). 25-OHD levels are used to determine vitamin D status. The second hydroxylation takes place in the kidneys forming the final active hormone 1, 25-$(OH)_2$ vitamin D [2]. Chronic renal failure affects not just the exocrine function of the kidneys, but also the endocrine function including activation of 25-OHD. In the general population deficiency of vitamin D has been associated with a higher risk of infections [3]. Among kidney transplant recipients some studies indicate a relevance of 25-OHD levels for infections overall [4], bacterial infections [5], urinary tract infections [6] and opportunistic viral infections [7]. Other studies could not identify an association between vitamin D status and infections after kidney transplantation [8]. Given the heterogeneity of these reported observations, we planned a study within the Swiss Transplant Cohort Study (STCS). In the present study, vitamin D levels at time of kidney transplantation and 6 months afterwards were assessed. In addition, we specifically addressed the question whether vitamin D status has an association with clinically relevant infections. For the most common infectious etiology, i.e. bacterial infections, a subgroup analysis was performed. For infections a total follow-up of 2.5 years was divided into two periods, the first 6 months post-transplant and after 6 months until 2.5 years post-transplant. Our analysis considered the vitamin D status at time of transplantation and at 6 months post-transplant for the first period and the second period, respectively.

Patients and Methods

Study design, participants and patient-related data

The present study was a nested project within the Swiss Transplant Cohort Study (STCS, www.stcs.ch). For the STCS data and biosamples from every transplant center in Switzerland, i.e. Basel, Bern, Geneva, St. Gallen, Lausanne and Zurich, are prospectively collected [9]. Approval of the STCS was provided by the corresponding Ethics Committees. From all enrolled patients informed consent was obtained prior to transplantation. Kidney transplantations of the analyzed

recipients were performed between May 2008 and March 2009. Except information about vitamin D supplementation, which was retrospectively added, all remaining data were prospectively gathered. Infectious diseases are prospectively recorded by dedicated professionals applying definitions established within the STCS and are supervised by transplant infectious diseases physicians. For the analyses of an association between vitamin D levels and infectious diseases exclusively symptomatic infections and, if possible, prompting targeted treatment, were considered. Clinical presentations with suspected infectious etiology resulting in initiation of antimicrobial treatment by the treating physicians, were considered as probable infections, if routine diagnostics failed to identify a causative pathogen. For the subgroup analysis of bacterial infections, we defined proven bacterial infections as clinically apparent infections combined with detection of the causative bacterium and initiation of targeted antimicrobial treatment, as previously described [10].

Determination of vitamin D levels

Prospectively, at time of transplant and 6 months afterwards, collected blood samples of the participants were retrieved from the STCS biobank and sent to the Institute of Clinical Chemistry of the University Hospital Zurich for centralized, uniform measurement. 25-OH vitamin D was measured with the Roche Diagnostics Vitamin D total assay on Cobas® 8000 (Roche Diagnostics, Mannheim, Germany).

25-OH vitamin D levels < 20ng/ml were categorized as deficiency, whereas 25-OH vitamin D levels ≥ 20ng/ml were judged as no deficiency [11].

Statistis

All statistical analyses were performed in R (version 3.3.2). For continuous variables median and interquartile ranges (IQR), for categorical variables absolute numbers and frequencies (%) were reported. All applied statistical tests were two-sided tests, *P*-values < 0.05 were considered significant. For comparison of continuous variables between two groups Wilcoxon rank-sum test was applied, whereas for pairwise comparisons Wilcoxon matched-pairs signed-rank test was used. For investigation of the association between vitamin D levels and infections, we defined two observation periods. The timespan from transplantation to 6 months post-transplant was referred as first period, for this analysis vitamin D determined at time of transplantation was taken into

account. The second period encompassed the timespan after 6 months until 30 months post-transplant; for this period, 25-OH vitamin D values measured at 6 months after transplantation were considered. Patients with shorter follow-up due to death or lost to follow-up were excluded from this analysis (1 out of 135 kidney recipients for the second period). For identification of risk factors associated with infections logistic regression was performed. In the univariable analysis, the variables vitamin D status (no deficiency vs. deficiency), age, sex, type of donation (deceased vs. living), induction immunosuppression, body mass index (BMI), and diabetic nephropathy as cause of end stage renal disease (ESRD) were tested. For the first period, vitamin D status, age, sex and induction immunosuppression, whereas vitamin D status, age and sex for the second period were included in the multivariable analyses. Additional variables were added to the multivariable model, if *P*-values reached ≤ 0.10 in univariable analysis

Results

Patients' characteristics

Participants were predominantly of Caucasian origin (124, 91.9%) with 90 (66.7%) males (Table 1). Median age was 51 years (IQR 40-62). The most frequent underlying diseases leading to renal failure were glomerulonephritis (32, 23.7%), polycystic kidney disease (27, 20.0%), nephrosclerosis (17, 12.6%) and diabetic nephropathy (12, 8.9%). One hundred and eight (80.0%) participants required renal replacement therapy prior to transplantation, 81 (60.0%) received hemodialysis and 27 (20.0%) peritoneal dialysis. In 77 (57.0%) patients living kidney transplantation was performed, whereas 58 (43.0%) received a graft from a deceased donor. Immunosuppressive therapy included induction therapy in 110 (81.5%) recipients. At time of transplantation in 61 (45.2%) participants supplementation therapy with cholecalciferol (median dose 800IU/day) and in another 37 (27.4%, in two individuals combined with cholecalciferol) participants with 1, 25-dihydroxycholecalciferol (median dose 0.25µg/day) was administered. Six months after transplantation 84 (62.2%) kidney recipients received cholecalciferol (median dose 800IU/day) and 5 (3.7%, in two individuals combined with cholecalciferol) patients 1, 25-dihydroxycholecalciferol (median dose 0.25µg/day).

Vitamin D status

Peri-transplant only a minority of kidney recipients had non deficient levels of 25-OHD (n=31, 23.0%) (Table 2). The majority of kidney transplant recipients showed deficient levels (n=104, 77.0%). Six months post-transplant, in 88 (65.2%) kidney transplant recipients vitamin D deficiency was present. A significant increase in 25-OHD levels between time of transplantation (median 12.0ng/ml, IQR 5.3-19.5ng/ml) and 6 months post-transplant (median 16.5ng/ml, IQR 10.6-22.6ng/ml) was detectable (*P*=0.005). Peri-transplant 19.4% of patients receiving supplementation treatment with vitamin D analogues had 25-OHD levels of at least 20ng/ml, whereas this proportion was 32.4% of patients without supplementation. Six months post-transplant 25-OHD levels were ≥ 20ng/ml in 46.0% of patients receiving supplementation therapy (vs. 10.3% in kidney recipients without supplementation therapy).

Vitamin D status and infections

Infections within the first 6 months post-transplant

In the first 6 months post-transplant a total of 155 infections affecting 75 (55.6%) participants were recorded, 78 (50.3%) infections were caused by bacteria, 31 (20.0%) infections by viruses and a much lower proportion by fungi (8, 5.2%) and parasites (2, 1.3%) (Table 3). In 36 (23.2%) episodes an infectious etiology was suspected and antimicrobial treatment administered, but identification of the causative organism failed (i.e. probable infections). The most frequent, by bacterial infections affected sites were the urinary tract (n=46, 59.0%), gastrointestinal tract (n=11, 14.1%), bacteremia (n=13, 12.8%) and respiratory tract (n=3, 3.8%) (Figure 1).

In univariable logistic regression we did not detect an association of infections with vitamin D, age, type of donation, induction immunosuppression, BMI and diabetic nephropathy as cause of ESRD, respectively (Table 4). Male sex tended to be associated with a lower odds for infections (odds ratio (OR) 0.50, 95%CI 0.24 to 1.05; *P*=0.068). In multivariable analysis male sex was significantly protective against infection (adjusted odds ratio (aOR) 0.46, 95%CI 0.22 to 0.99; *P*=0.047), whereas increasing age showed a trend of higher risk (aOR 1.24, 95%CI 0.96 to 1.60; *P*=0.096) (Table 4).

If we focused exclusively on bacterial infections, aging correlated positively with bacterial infections (OR 1.33, 95%CI 1.03 to 1.72; *P*=0.030) (Table 5). Male sex showed a trend of protection (OR 0.48, 95%CI 0.23 to 1.02; *P*=0.055), whereas no association was observed for

vitamin D, type of donation, induction immunosuppression and BMI. Diabetic nephropathy as etiology of ESRD tended to be associated with a higher risk of bacterial infections (OR 3.13, 95%CI 0.93 to 10.50; *P*=0.064). Multivariable logistic regression confirmed increasing age as risk factor (aOR 1.39, 95%CI 1.03 to 1.87; *P*=0.031) and the protective effect of male sex (aOR 0.42, 95%CI 0.19 to 0.92; *P*=0.033).

Infections after 6 up to 30 months post-transplant

After 6 until 30 months post-transplant, totally 168 infections occurring in 70 (51.9%) of participants were observed. 78 (46.4%) infections were caused by bacteria, 34 (20.2%) by viruses, 3 (1.8%) by fungi and 4 (2.4%) by parasites (Table 3). In 49 (29.2%) episodes identification of a causative pathogen failed, but an antimicrobial therapy initiated. Bacterial infections most frequently were urinary tract infections (n = 53, 68.0%), gastrointestinal infections (n = 6, 7.7%), respiratory tract infections (n = 6, 7.7%) or bacteremia (n = 4, 5.1%) (Figure 1).
Univariable logistic regression showed a trend of a reduced odds of infection for male sex (OR 0.49, 95%CI 0.23 to 1.03; *P*=0.058), which was also present in multivariable analysis (aOR 0.50, 95%CI 0.23 to 1.07; *P*=0.074), whereas no association was detected for other variables (Table 4). Analysis of bacterial infections solely indicated a protective effect of male sex for infections (univariable OR 0.42, 95%CI 0.20 to 0.89; *P*=0.025; multivariable aOR 0.41, 95%CI 0.19 to 0.88; *P* = 0.022). We did not detect an association between vitamin D levels and bacterial infections in the second period after kidney transplantation (Table 5).

Discussion

In the present study vitamin D levels of kidney allograft recipients were determined by uniform measurement using prospectively collected samples at the time of transplantation and 6 months thereafter. Vitamin D deficiency was highly prevalent at time of transplantation, and 6 months after transplantation still more than half of transplant recipients did not have sufficient 25-OHD levels. Our analyses did not detect a significant association between vitamin D status and clinically relevant infections and bacterial infections for both observation periods, respectively. The finding of common vitamin D deficiency is likely due to multiple factors. Supplementation strategies could have been suboptimal. Kidney transplant recipients might require increased doses

of vitamin D to gain sufficient 25-OHD levels. Post-transplant alterations of specific pathways influencing vitamin D metabolism may be relevant. Such, higher levels of fibroblast growth factor 23 (FGF-23) have been demonstrated following kidney transplantation [12]. FGF-23 inhibits 1-position hydroxylation of 25-OHD and promotes degradation of 1, 25-$(OH)_2$ vitamin D [13], which could contribute to an increased requirement of supplementation. Further, transplant recipients avoid sun exposure with respect to the increased risk of skin cancer in the context of immunosuppressive treatment.

In literature, hypotheses for the relevance of vitamin D in infections have been generated. Monocytes and macrophages can produce the active form of vitamin D, i.e. 1, 25-$(OH)_2$ vitamin D, via CYP27B1-hydroxylase requiring circulating 25-OHD as substrate. Vitamin D receptor-directed genes, e.g. cathelicidin, are activated by 1, 25-$(OH)_2$ vitamin D triggering killing of ingested pathogens [14,15]. LL-37, which is the active form of cathelicidin, has the capability to break bacterial membranes and viral envelopes [16]. Beyond, increasing evidence indicates presence of this pathway in barriers like skin [17], gut [18] and lung [19]. Insufficient 25-OHD levels might impede this pathway. In our multicenter study with prospectively collected data and uniform 25-OHD measurement, we were not able to detect a correlation of vitamin D status with clinically relevant infections or bacterial infections. Notably, also in an additional analysis on opportunistic infections we could not detect an association with vitamin D status (Supplemental Table). These findings are in line with the results of Ban Th et al [8,20]. Few studies, most of them based on retrospective data collection, reported an association between vitamin D deficiency and infections [4,6,21]. The cut-off value used for definition of vitamin D deficiency in our study is based on studies that considered dynamics in bone turnover variables [11]. Up to now, no cut-off has been specifically established for infectious risk stratification by vitamin D status. Notably, in an analysis considering vitamin D levels as continuous variable, we also did not detect an association with infections (data not shown). It can be speculated that there might be a publication bias in this context with a relevant number of negative studies unpublished. In the first observation period male sex was associated with a protective effect from both, clinically relevant infections and bacterial infections. In the second observation period this effect was only observed for bacterial infections. This observation might be also due to the high frequency of urinary tract infections and the fact that urinary tract infections are more common in females [22].

Limitations of our study are the limited number of participants and the retrospective collection of information on vitamin D supplementation. Furthermore, we did not collect information on the need of hospitalization due to an infection thus hindering an analysis addressing the question of a difference in severity of infectious disease events by vitamin D status. Strengths include serial, uniform measurements of 25-OHD, the cohort study design with follow-up data up to 2.5 years post-transplant for the vast majority of patients (99.3%).

To conclude, our study showed a relevant proportion of participants remaining vitamin D deficient despite a high frequency of supplementation. Our findings do not support a relevant role of vitamin D in infections after kidney transplantation.

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Disclosures

All authors declare no conflicts of interest. This study was performed in the framework of the Swiss Transplant Cohort Study, supported by the Swiss National Science Foundation, the Swiss University Hospitals (G15) and transplant centers.

Author contributions:

PWS contributed to data collection, performed data analysis, interpreted the data and drafted the manuscript.

KK contributed to data analysis.

HAB, TF, CG, HHH, PM contributed to the trial design.

LS performed 25-OH vitamin D measurement.

CVD, OM, MW contributed to the trial design and data acquisition.

KB, MB, NE, CH contributed to data acquisition.

NJM designed the trial, contributed to data analysis, interpretation of the results and writing of the manuscript.

All authors critically reviewed the article and approved the final version of the article.

References:

1. Sadlier DM, Magee CC. Prevalence of 25(OH) vitamin D (calcidiol) deficiency at time of renal transplantation: a prospective study. *Clinical transplantation.* 2007;21(6):683-688.
2. Holick MF. Vitamin D status: measurement, interpretation, and clinical application. *Annals of epidemiology.* 2009;19(2):73-78.
3. Ginde AA, Mansbach JM, Camargo CA, Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Archives of internal medicine.* 2009;169(4):384-390.
4. Kalluri HV, Sacha LM, Ingemi AI, et al. Low vitamin D exposure is associated with higher risk of infection in renal transplant recipients. *Clinical transplantation.* 2017;31(5).
5. Park YJ, Kim SU, Lee KH, et al. Vitamin D deficiency is associated with increased risk of bacterial infections after kidney transplantation. *The Korean journal of internal medicine.* 2017;32(3):505-513.
6. Kwon YE, Kim H, Oh HJ, et al. Vitamin D deficiency is an independent risk factor for urinary tract infections after renal transplants. *Medicine.* 2015;94(9):e594.
7. Rech MA, Fleming JN, Moore CL. 25-hydroxyvitamin D deficiency and opportunistic viral infections after kidney transplant. *Experimental and clinical transplantation : official journal of the Middle East Society for Organ Transplantation.* 2014;12(2):95-100.
8. Lee JR, Dadhania D, August P, Lee JB, Suthanthiran M, Muthukumar T. Circulating levels of 25-hydroxyvitamin D and acute cellular rejection in kidney allograft recipients. *Transplantation.* 2014;98(3):292-299.
9. Koller MT, van Delden C, Muller NJ, et al. Design and methodology of the Swiss Transplant Cohort Study (STCS): a comprehensive prospective nationwide long-term follow-up cohort. *European journal of epidemiology.* 2013;28(4):347-355.
10. Schreiber PW, Bischoff-Ferrari HA, Boggian K, et al. Vitamin D status and risk of infections after liver transplantation in the Swiss Transplant Cohort Study. *Transplant international : official journal of the European Society for Organ Transplantation.* 2019;32(1):49-58.
11. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism.* 2011;96(7):1911-1930.

12. Baia LC, Humalda JK, Vervloet MG, Navis G, Bakker SJ, de Borst MH. Fibroblast growth factor 23 and cardiovascular mortality after kidney transplantation. *Clinical journal of the American Society of Nephrology : CJASN.* 2013;8(11):1968-1978.
13. Shimada T, Hasegawa H, Yamazaki Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2004;19(3):429-435.
14. Adams JS, Hewison M. Update in vitamin D. *The Journal of clinical endocrinology and metabolism.* 2010;95(2):471-478.
15. Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: vitamin D-mediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin. *Journal of immunology (Baltimore, Md : 1950).* 2007;179(4):2060-2063.
16. Braff MH, Gallo RL. Antimicrobial peptides: an essential component of the skin defensive barrier. *Current topics in microbiology and immunology.* 2006;306:91-110.
17. Frohm Nilsson M, Sandstedt B, Sorensen O, Weber G, Borregaard N, Stahle-Backdahl M. The human cationic antimicrobial protein (hCAP18), a peptide antibiotic, is widely expressed in human squamous epithelia and colocalizes with interleukin-6. *Infection and immunity.* 1999;67(5):2561-2566.
18. Liu N, Nguyen L, Chun RF, et al. Altered endocrine and autocrine metabolism of vitamin D in a mouse model of gastrointestinal inflammation. *Endocrinology.* 2008;149(10):4799-4808.
19. Hansdottir S, Monick MM, Hinde SL, Lovan N, Look DC, Hunninghake GW. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. *Journal of immunology (Baltimore, Md : 1950).* 2008;181(10):7090-7099.
20. Ban TH, Kim JH, Jang HB, et al. Clinical effects of pre-transplant serum 25-hydroxyvitamin D level on post-transplant immunologic and non-immunologic outcomes in kidney transplant recipients. *Transplant immunology.* 2017;40:51-56.
21. Fernandez-Ruiz M, Corbella L, Morales-Cartagena A, et al. Vitamin D deficiency and infection risk in kidney transplant recipients: A single-center cohort study. *Transplant infectious disease : an official journal of the Transplantation Society.* 2018:e12988.
22. Gupta K, Grigoryan L, Trautner B. Urinary Tract Infection. *Annals of internal medicine.* 2017;167(7):Itc49-itc64.

Tables:

Table 1: Baseline characteristics

Variable	
Age (median (IQR))	51y (40, 62)
Sex (n, %)	Male 90 (66.7%) Female 45 (33.3%)
Ethnicity (n, %)	Caucasian 124 (91.9%) African 5 (3.7%) Asian 5 (3.7%) American Indian 1 (0.7%)
Underlying disease (n, %)	Glomerulonephritis 32 (23.7%) Polycystic kidney disease 27 (20.0%) Nephrosclerosis 17 (12.6%) Diabetic nephropathy 12 (8.9%) Reflux nephropathy 9 (6.7%) Cause unknown 12 (8.9%) Other 26 (19.3%)
Renal replacement therapy (n, %)	HD: 81 (60.0%) PD: 27 (20.0%) None: 27 (20.0%)
Type of donation (n, %)	DBD 58 (43.0%) living related 39 (28.9%) living unrelated 38 (28.1%)
Induction therapy (n, %)	Basiliximab 89 (65.9%) (7 combined with Anti-T-lymphocyte-immunoglobulin) Anti-T-lymphocyte-immunoglobulin 10 (7.4%) (4 combined with IVIG) Rituximab 4 (3.0%) Other regimen 7 (5.2%) None 25 (18.5%)
Maintenance immunosuppression* (n, %)	Tac+MMF+steroids 60 (44%) Tac+EC-MPA+steroids 17 (12.6%) Tac+MMF 9 (6.7%) Tac+EC-MPA 9 (6.7%) CsA+MMF+steroids 20 (14.8%) CsA+EC-MPA+steroids 8 (5.9%) Other regimen 12 (8.9%)

Supplementation of vitamin D (n, %)	peri-transplant) cholecalciferol 61 (45.2%) 1, 25-dihydroxycholecalciferol 37** (27.4%) 6 months post-transplant cholecalciferol 84 (62.2%) 1, 25-dihydroxycholecalciferol 5*** (3.7%)

* 6 months after transplantation

** in 2 participants supplementation with cholecalciferol and 1, 25-dihydroxycholecalciferol

*** in 2 participants supplementation with cholecalciferol and 1, 25-dihydroxycholecalciferol

Abbreviations: CsA: cyclosporine A, DBD: donation after brain death, EC-MPA: enteric-coated mycophenolate, HD: hemodialysis, IVIG: intravenous immunoglobulins, MMF: mycophenolate mofetil, PD: peritoneal dialysis, RRT: renal replacement therapy, Tac: tacrolimus

Table 2: Vitamin D status peri-transplant and 6 months after transplantation

Vitamin D status	Peri-transplant	6 months post-transplant*
Deficiency	104 (77.0%)	88 (65.2%)
No deficiency	31 (23.0%)	46 (34.1%)

* one measurement failed due to technical issues

Table 3: Infections in the first 6 months after transplantation and 6 to 30 months after transplantation

Period	Pathogen	Site of infection	Bacterial/viral/fungal/parasitic species
First 6 months post-transplant	Bacterial infection* (n=78)	Urinary tract (n=46) Gastrointestinal tract (n=11) Bacteremia (n=13) Respiratory tract (n=3) Other (n=5)	*Escherichia coli* (n=32) *Enterococcus* spp. (n=23) *Klebsiella* spp. (n=10) Coagulase negative staphylococci (n=11) *Clostridium* spp. (n=5) Other gram-positive bacteria (n=4) Other gram-negative bacteria (n=2) Other bacteria (n=6)
	Viral infection (n=31)	Mucocutaneous (n=9) Viremia (n=8) Respiratory tract (n=5) Urinary tract (n=4) Gastrointestinal tract (n=3) Other (n=2)	BK virus (n=9) Human herpes virus 1/2 (n=8) Cytomegalovirus (n=3) Varicella zoster virus (n=2) Respiratory viruses (n=5) Other viruses (n=4)
	Fungal infection (n=8)	Mucocutaneous (n=4) Gastrointestinal tract (n=2) Respiratory tract (n=1) Urinary tract (n=1)	*Candida albicans* (n=4) *Aspergillus fumigatus* (n=1) Not identified (n=3)
	Parasitic infection (n=2)	Gastrointestinal tract (n=2)	Not specified (n=2)
	Probable infection (n=36)	Respiratory tract (n=18) Mucocutaneous (n=8) Gastrointestinal tract (n=4) Urinary tract (n=4) Other sites (n=2)	Not identified (n=36)
6 to 30 months post-transplant	Bacterial infection** (n=78)	Urinary tract (n=53) Gastrointestinal tract (n=6) Respiratory tract (n=6) Bacteremia (n=4) Mucocutaneous (n=4) Bone infection (n=3) Other (n=2)	*Escherichia coli* (n=35) *Enterococcus* spp. (n=6) *Staphylococcus aureus* (n=5) *Klebsiella* spp. (n=9) Other Enterobacteriaceae (n=6) Other gram-positive bacteria (n=5) Other gram-negative bacteria (n=4) Other bacteria (n=13)
	Viral infection (n=34)	Gastrointestinal tract (n=10) Mucocutaneous (n=8)	Cytomegalovirus (n=8) BK virus (n=4)

		Viremia (n=8) Respiratory tract (n=4) Urinary tract (n=3) Other site (n=1)	Human herpes virus 1/2 (n=5) Varicella zoster virus (n=4) Respiratory viruses (n=4) Gastrointestinal viruses (n=9)
	Fungal infection (n=3)	Mucocutaneous (n=1) Respiratory tract (n=1) Other site (n=1)	*Candida albicans* (n=1) *Pneumocystis* sp. (n=1) Other fungi (n=1)
	Parasitic infection (n=4)	Skin (n=3) Other site (n=1)	Not specified (n=4)
	Probable infection (n=49)	Respiratory tract (n=13) Gastrointestinal tract (n=11) Urinary tract (n=8) Mucocutaneous (n=6) Bacteremia (n=2) Other sites (n=9)	Not identified (n=49)

* 15 infections with detection of two bacterial species

** 5 infections with detection of two bacterial species

Table 4: Logistic regression analysis of risk for infections within the first 6 months post-transplant and after 6 up to 30 months post-transplant

	first 6 months post-transplant				after 6 up to 30 months post-transplant			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	Odds ratio (95%CI)	*P*	Odds ratio (95%CI)	*P*	Odds ratio (95%CI)	*P*	Odds ratio (95%CI)	*P*
Vitamin D status								
No deficiency	Reference		Reference		Reference		Reference	
Deficiency	0.88 (0.39 to 1.97)	0.749	1.05 (0.44 to 2.51)	0.916	0.75 (0.37 to 1.54)	0.157	0.67 (0.31 to 1.43)	0.299
Age								
Per decade increase	1.19 (0.95 to 1.48)	0.128	1.24 (0.96 to 1.60)	0.096	0.89 (0.71 to 1.10)	0.278	0.85 (0.67 to 1.07)	0.168
Sex								
Female	Reference		Reference		Reference		Reference	
Male	0.50 (0.24 to 1.05)	0.068	0.46 (0.22 to 0.99)	0.047	0.49 (0.23 to 1.03)	0.058	0.50 (0.23 to 1.07)	0.074
Type of donation								
Living	Reference				Reference			
Deceased	1.41 (0.71 to 2.81)	0.332			0.99 (0.50 to 1.98)	0.985		
Induction immunosuppression								
None	Reference		Reference		Reference			
Any	1.19 (0.50 to 2.85)	0.692	0.85 (0.32 to 2.25)	0.743	0.99 (0.42 to 2.37)	0.989		
BMI*								
Per point increase	1.01 (0.94 to 1.09)	0.764			0.97 (0.90 to 1.04)	0.421		
Etiology of ESRD								

Any other etiology	Reference			Reference		Reference	
Diabetic nephropathy	2.59 (0.67 to 10.03)	0.168		3.10 (0.80 to 12.01)	0.101	3.15 (0.78 to 12.70)	0.106

* BMI (body mass index) determined at time of transplantation and at 6 months post-transplant used for analysis of ~~incident~~ infections within first 6 months post-transplant and after 6 up to 30 months post-transplant, respectively

ESRD: end stage renal disease

Table 5: Logistic regression analysis of risk for bacterial infections within the first 6 months post-transplant and after 6 up to 30 months post-transplant

	first 6 months post-transplant				after 6 up to 30 months post-transplant			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	Odds ratio (95%CI)	*P*	Odds ratio (95%CI)	*P*	Odds ratio (95%CI)	*P*	Odds ratio (95%CI)	*P*
Vitamin D status								
No deficiency	Reference		Reference		Reference		Reference	
Deficiency	0.62 (0.27 to 1.41)	0.249	0.79 (0.32 to 1.96)	0.608	0.84 (0.40 to 1.80)	0.660	0.79 (0.35 to 1.75)	0.557
Age								
Per decade increase	1.33 (1.03 to 1.72)	0.030	1.39 (1.03 to 1.87)	0.033	1.01 (0.80 to 1.27)	0.966	1.01 (0.79 to 1.29)	0.929
Sex								
Female	Reference		Reference		Reference		Reference	
Male	0.48 (0.23 to 1.02)	0.055	0.42 (0.19 to 0.92)	0.031	0.42 (0.20 to 0.89)	0.025	0.41 (0.19 to 0.88)	0.022
Type of donation								
Living	Reference				Reference			
Deceased	1.25 (0.61 to 2.58)	0.539			0.99 (0.47 to 2.06)	0.969		
Induction immunosuppression								
None	Reference		Reference		Reference			
Any	1.08 (0.43 to 2.73)	0.876	0.62 (0.21 to 1.81)	0.383	2.17 (0.76 to 6.25)	0.150		
BMI*								
Per point increase	1.03 (0.95 to 1.11)	0.464			0.99 (0.92 to 1.07)	0.841		
Etiology of ESRD								

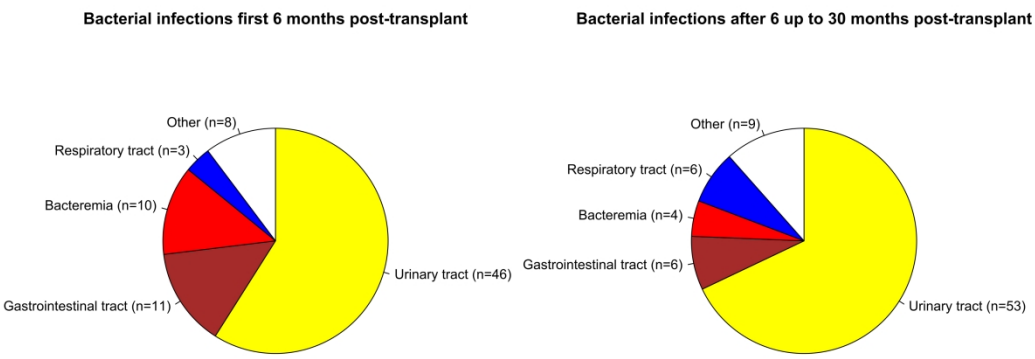
Any other etiology	Reference		Reference		Reference	
Diabetic nephropathy	3.13 (0.93 to 10.50)	0.064	2.44 (0.70 to 8.53)	0.163	2.27 (0.69 to 7.51)	0.179

* BMI (body mass index) determined at time of transplantation and at 6 months post-transplant used for analysis of ~~incident~~ infections within first 6 months post-transplant and after 6 up to 30 months post-transplant, respectively

ESRD: end stage renal disease

Figure Legends:

Figure 1: Site of infection in proven bacterial infections in the first period (first 6 months after transplantation) and second period (after 6 up to 30 months after transplantation), respectively



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